Please cancel claims 18-24 without prejudice, and amend claims 1, 5, 13, 14 and 15 as presented in Appendix A (attached hereto). A marked-up version of the revised claims showing the changes made is attached hereto as Appendix B.

REMARKS

Status of the Application

At the time the Office Action was mailed, claims 1-24 were pending in the application. Claim 18 was rejected under 35 U.S.C. 102(b). Claims 1-17 and 19-24 were rejected under 35 U.S.C. 103. No claims were allowed.

Upon entry of this amendment, claims 1, 5, 13, 14 and 15 will have been amended, and claims 18-24 will have been cancelled. Therefore claims 1-17 remain before the examiner for consideration.

Rejection Under 35 U.S.C. 102(b)

Claim 18 was rejected as being anticipated by Wheeler et al., for reasons set forth in the Office Action of February 27, 2002. Claim 18 having been cancelled by this amendment, this rejection is rendered moot. Therefore withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. 103

Claims 1-17 and 19-24 were rejected under 35 U.S.C. 103 as being unpatentable over Wen et al. (U.S. Patent 6,066,675) ("Wen") and Sallman et al. (U.S. Patent No. 5,891,913) ("Sallman"). Applicants note that although the Office Action refers to "Steinberg et al.," a

telephone conference with the examiner on September 25, 2002 clarified and confirmed that "Steinberg et al." refers to Wen. For purposes of this response, reference is made only to Wen.

According to the Office Action, Wen et al. "teach the use of brimonidine and fibroblast growth for the treatment of diseases or conditions caused by injury or death of retinal photoreceptors." It is further stated that it would have been obvious to add "non-steroidal anti-inflammatory agents to brimonidine," (referring to Sallman), for reasons mentioned in the previous Office Action.

Upon entry of this amendment, claim 1 will have been amended to recite "a method of treating a retinal disease or condition, which disease or condition is caused by damage, disruption, or degeneration of an RPE cell or a Muller cell." Applicants respectfully disagree that it would have been obvious from the teachings of Wen to use brimonidine for treatment of retinal conditions caused by damage, disruption, or degeneration of RPE or Muller cells, for the reasons set forth below.

Retinal Degeneration Is Caused By Many Different Mechanisms

The Office Action asserts that the Wen reference "makes clear that brimonidine and growth factor have been previously used for the treatment of conditions caused by the injury or death to the retinal photoreceptors." Although it is unstated, the Office Action apparently assumes that it would have been obvious to those in the field of photoreceptor degeneration to treat any condition caused by injury or death of the photoreceptors with brimonidine, given the teachings of Wen. However, it was well known in the art at the time of the applicants' invention that there are myriad causes of photoreceptor degeneration. Most of them are hereditary, involving mutations in specific genes of the photoreceptors and retinal pigment epithelial (RPE) cells that are responsible for essential functions within these cells. (See, e.g., Sullivan LS and

Daiger SP, Inherited retinal degeneration: exceptional genetic and clinical heterogeneity, Mol. Med. Today 2: 380-386, 1996.) Given the myriad causes of photoreceptor degeneration, those of skill in the art would not have expected a single agent to cure all of these diseases and disorders.

The Wen patent demonstrated a protective effect of two agents, i.e., clonidine and xylazine in photoreceptors damaged by one mechanism alone, i.e., excessive light. The Wen results were obtained utilizing a well known light damage model of retinal degeneration in which photoreceptor degeneration is induced by exposing the retina to very high light levels not naturally experienced by photoreceptors. As discussed previously in applicant's response dated May 14, 2002 to the Office Action of February 27, 2002, the Wen results showed that the rate of photoreceptor degeneration in this particular experimental model was reduced in rats injected with xylazine or clonidine prior to damaging light exposure. No other models of retinal degeneration were tested.

Brimonidine Promotes Normal Retinal Structure and Function in Retinas Deprived of RPE

The studies described in Wen are in marked contrast to those performed by the applicants. In applicants' experiments, damage to the retina was inflicted by detachment of the retina from its underlying supportive layer, i.e., the RPE. It is well known that RPE cells provide essential support for the photoreceptors, and that damage of the RPE cells can result in photoreceptor death. The experiments in Wen were not performed using retinas deprived of the RPE. Rather the damage was directly inflicted on the photoreceptors, using excessive light.

The remarkable effect of brimonidine in applicant's system was to promote normal retinal structure and function in absence of the RPE. This is evidenced in the specification by support of membrane assembly and production of opsin by photoreceptors, in absence of RPE, but in the presence of brimonidine. Compare e.g., Figs. 3A, 4A and 5A of the application, reproduced

herein and attached as "Exhibit A." Exhibit A shows normal retinal architecture in the presence of RPE (Fig. 3A), degeneration in the absence of RPE (Fig. 4A) and nearly normal architecture in the absence of RPE, following brimonidine treatment (Fig. 5A). Further evidence of normal retinal architecture and gene expression was exhibited by the Muller cells of brimonidine-treated retinas devoid of RPE. (See Figs. 7,8.)

Applicants' results show that brimonidine restored normal retinal architecture, expression of opsin by photoreceptors and normal expression of Muller cell markers following separation of the retina from the RPE. As stated in the specification on p. 20, lines 27-29, applicants' work demonstrates that "brimonidine may be an effective therapeutic agent for certain forms of retinal degenerations and other conditions where disruption of RPE integrity may lead to permanent loss of photoreceptor function." Such conditions are described in the specification (§§ 4.4.2 - 4.4.4) and include but are not limited to photoreceptor degeneration resulting from removal of the RPE (e.g., by retinal detachment), photoreceptor degeneration resulting from mutations in RPE genes, and age-related macular degeneration. Claims 1, 5, 13, 14 and 15 have been amended to clarify applicants' discovery of the types of retinal damage or degeneration that can be treated with brimonidine and related compounds.

The Office Action asserts that Sallman teaches the use of secondary active ingredients, wetting agents and ophthalmic carriers in an ophthalmic formulation for treatment of inflammatory conditions of the eye. In view of the inapplicability of the primary reference (i.e., Wen) to conditions caused by damage, disruption, or degeneration of the RPE or Muller cells, the rejection under 35 U.S.C. 103 based on the combination of Wen and Sallman is rendered moot.

Conclusion

The currently pending claims are supported throughout the specification and are patentable over the prior art. No new matter has been added. This application is now in full condition for allowance, and such action is respectfully requested.

A petition for a two month retroactive extension of time and the required fee are enclosed. The Commissioner is hereby authorized to charge any underpayment or credit any overpayment of fees under 37 C.F.R. 1.16 or 1.17 as required by this paper to Deposit Account 50-0951.

The examiner is cordially invited to call the undersigned if clarification is needed on any matter within this amendment, or if the examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

AKERMAN SENTERFITT

Dated: February 11, 2003

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Docket No: 6704-11